

Describe the functionality of the of water structure-making substance. No new matter has been added by these amendments.

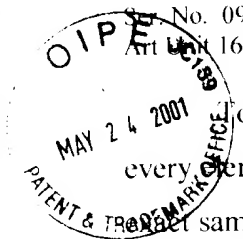
4. The Official Action dated November 21, 2000, rejected claims 1, 6, 14, 16, 21, 29, 31 and 32 under 35 U.S.C. §102(a), stating that the claimed invention was anticipated by Robles et al., (J. Am. Chem. Soc., 1996, Vol. 118, No.24, pages 5820-5821). These rejections under §102(a) are respectfully traversed for the following reasons.

To properly support a rejection under §102(a), a cited reference must disclose each and every element of the claimed invention, and each element must perform the same function in the exact same way as the claimed invention. The Robles et al., reference uses different substances, at different concentrations, which stabilize the DNA triplexes in a different way.

The Official Action states that Robles et al., "teach stabilization of DNA triplexes by adding ethylene glycol". Robles et al. do not "add" the glycol. Robles et al., must synthetically link the glycol to the third strand of DNA and to a benzimidazol fluorescent dye (Hoechst 33258). (See, Robles et al., and Declaration of Jacques Fresco). It is this dye, binding in the minor groove, that supplies stability. (See, Declaration of Jacques Fresco). Since the glycol is covalently linked to the third strand, it is present in concentrations too low to effect triplex stability on its own. (See Declaration of Dr. Fresco). The present invention stabilizes triplex DNA using only the water structure-making substances, such as poly(ethylene glycol), whereas Robles et al., use hexa(ethylene glycol) as a linker for the minor groove binding dye, where the dye provides any stability effects. (See, Declaration of Jacques Fresco). No triplex stabilization is attributed to, or evidenced by, the glycol by Robles et al. (See, Declaration of Jacques Fresco).

Therefore, in view of the above amendments, remarks, and the Declaration of Jacques Fresco, the rejection of Claims 1, 6, 14, 16, 21, and 29 is rendered moot. Applicants respectfully requested reconsideration of the application, withdrawal of all rejections, and that claims 1-32 be allowed to issue at an early date.

5. The Official Action dated November 21, 2000, rejected claims 1, 2, 4, 5, 14, 16, 17, 19, 20, and 29 under 35 U.S.C. §102(b), stating that the claimed invention was anticipated by Kiyama et al., (Nucleic Acids Research, 1995 Feb 11, Vol. 23, No. 3, pages 452-458). These rejections under §102(b) are respectfully traversed for the following reasons.



To properly support a rejection under §102(b), a cited reference must disclose each and every element of the claimed invention, and each element must perform the same function in the exact same way as the claimed invention. The Kiyama et al., reference uses different concentrations of stabilizing substances, which stabilize the DNA triplexes in a different way.

The Official Action states that Kiyama et al., "teach the stabilization of . . . triplexes in the presence of a cationic detergent. . .". The present invention stabilizes triplex DNA using much higher concentrations of water structure-making substances to change the structure of the water in the solution to enhance major groove binding by effectively reducing the amount of water displacement needed at the major groove. (See, Declaration of Jacques Fresco). Kiyama et al., do not use the water structure-making properties of the substances but rely on repulsing phosphite groups. (See, Declaration of Jacques Fresco). Furthermore the concentrations of the stabilizing substances used by Kiyama, et al., [ $10^{-4}$  Molar] are too low to demonstrate the water - structure-making activity used in the present invention. (See, Declaration of Jacques Fresco).

Therefore, in view of the above amendments, remarks, and the Declaration of Jacques Fresco, the rejection of Claims 1, 2, 4, 5, 14, 16, 17, 19, 20, and 29 is rendered moot. Applicants respectfully requested reconsideration of the application, withdrawal of all rejections, and that claims 1-32 be allowed to issue at an early date.

6. The Official Action dated November 21, 2000, rejected claims 1, 11-14, 16, and 26-29 under 35 U.S.C. §102(b), stating that the claimed invention was anticipated by D'Souza et al., (Bioorganic and Medicinal Chemistry Letters, 1994, Vol. 4, No. 8, pages 965-970). These rejections under §102(b) are respectfully traversed for the following reasons.

To properly support a rejection under §102(b), a cited reference must disclose each and every element of the claimed invention, and each element must perform the same function in the exact same way as the claimed invention. The D'Souza et al., reference uses different concentrations of stabilizing substances, which stabilize different helices in a different way, and, actually teach the destabilization.

The Official Action states that D'Souza et al., "teaches that 'Ethanol is known to increase stability of the complexation of a T15 third strand with duplex DNA in termolecular triple helices' and further teaches 'the stabilization has been attributed to the fact that B-form duplex

DNA changes conformation to A form at high ethanol concentrations...added ethanol favors the triplex by stabilizing this conformation" to counter Applicants' showing that D'Souza et al., describe that ethanol destabilized triple helices. It is the paragraph *before* the paragraph cited in the Office Action that states D'Souza's surprise that the ethanol actually **destabilized** the triple helices in view of the view stated in the cited, following paragraph. (See, Declaration of Jacques Fresco). D'Souza et al. show that use of ethanol destabilizes third strand binding, and make no mention of ethanol or any other water structure-making substances that stabilize triplexes. (See, Declaration of Jacques Fresco). D'Souza et al., describe that ethanol destabilizes triple helices in which a circle containing two pyrimidine sequence elements bind to a homopurine single strand sequence. They attribute this behavior to the enhanced inter-strand charge repulsion due to the effect of ethanol on the dielectric constant of the medium. There is no mention of any effect on the structure of water. This effect of ethanol is opposite to the ethanol solvent effect of the present invention. (See, Declaration of Jacques Fresco)

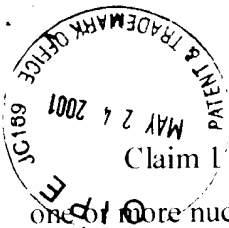
Therefore, in view of the above amendments, remarks, and the Declaration of Jacques Fresco, the rejection of Claims 1, 11-14, 16, and 26-29 is rendered moot. Applicants respectfully requested reconsideration of the application, withdrawal of all rejections, and that claims 1-32 be allowed to issue at an early date.

7. The Official Action dated November 21, 2000, rejected claims 1, 14-16, and 29-30 under 35 U.S.C. §102(b), stating that the claimed invention was anticipated by Shimizu et al., (Biochemistry, 18 Jan 1994, Vol. 33, No. 2, pages 606-613).. These rejections under §102(b) are respectfully traversed for the following reasons.

To properly support a rejection under §102(b), a cited reference must disclose each and every element of the claimed invention, and each element must perform the same function in the exact same way as the claimed invention. The Shimizu et al., reference uses different stabilizing substances, which stabilize in a different way and to a different (lower) degree..

The Official Action states that Shimizu et al., uses 1M NaCl as a water structure-making material". As shown in the application NaCl is not a water structure-making material, even at concentrations up to 6M. (See, specification at Table 1-17, page 19 and the Declaration of Jacques Fresco). The use of NaCl attributed to Shimizu et al., in the Office Action could not provide the enhanced triplex stability of the present invention.

Therefore, in view of the above amendments, remarks, and the Declaration of Jacques Fresco, the rejection of Claims 1, 14-16, and 29-30 is rendered moot. Applicants respectfully requested reconsideration of the application, withdrawal of all rejections, and that claims 1-32 be allowed to issue at an early date.



### Version Of Claims Showing Amendments Made

Claim 1 (Twice Amended) A method for enhancing the stability of a triplex formed from one or more nucleic acid strands in a solution, said method comprising adding to the solution in greater than a stoichiometric amount, either before or after formation of the triplex, [an effective amount for triplex stabilization], of either of the following:

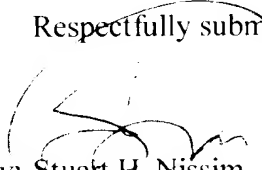
(a) a water structure-making substance other than an alkali or alkaline earth metal cation, a tetramethylammonium cation, or a polyamine; or

(b) a combination of said water structure-making substance and an alkali or alkaline earth metal cation, a tetramethylammonium cation, or a polyamine.

Claim 31 (Once amended) The method of claim 1, wherein the greater than a stoichiometric amount of the water structure-making substance enhances triplex by effectively decreasing the amount of water at the site of triplex formation. [is covalently linked to the third strand],

Claim 32 (Once amended) The method of claim 16, wherein the greater than a stoichiometric amount of the water structure-making substance enhances triplex by effectively decreasing the amount of water at the site of triplex formation. [is covalently linked to the third strand].

Respectfully submitted,

  
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